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The Respiratory Tract as a Route of Exposure

I. Major surfaces of the body: skin, respiratory tract, gastrointestinal tract.

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C. Basic anatomy and histology of the respiratory tract.

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I. The Respiratory Tract

Human lung surfaces, because of their primary function of gas exchange, are brought into intimate contact with irritating gases and airborne particles. The mass of air we inhale each day far exceeds the mass of material entering into our GI tract. The same thinness and extensive area that qualify the air-blood barrier for the rapid exchange of oxygen and carbon dioxide reduce its effectiveness as a barrier to inhaled micro-organisms, allergens, carcinogens, toxic particles, and noxious gases. Inhalation of these agents can initiate or at least aggravate chronic obstructive lung disease. Particularly in the cases of cigarette smoking and occupational exposures, the health consequences of particle deposition and toxic gas uptake are increasingly being demonstrated. To assess adequately the risk of a particular exposure, an understanding of the factors involved in the deposition and clearance of inhaled substances is needed. Therefore, the mechanisms which are pertinent to particle deposition and clearance will be described, and the relationship of these respiratory defense mechanisms to the pathogenesis of lung disease will be presented.

II. Review of Deposition:

A. Deposition is the process that determines what fraction of inspired particulates will be caught in the respiratory tract and thus fail to exit with the expired air. Several distinct processes following physical laws operate to move particles suspended in the inspired air toward the surface of the respiratory tract: inertial forces, sedimentation, Brownian diffusion, and interception. It is likely that all particles deposit upon touching a surface, and thus the site of initial deposition is the site of contact.

1. Inertia refers to the tendency of moving particles to resist changes in direction and speed. Repeated branching in the airways cause sudden changes in the direction of air-flow; however, because of inertia, particles tend to continue in their original direction, crossing air-flow streamlines and eventually impacting on the airway walls.

2. Gravity accelerates falling bodies downward, and terminal settling velocity is reached when viscous resistive forces are equal and opposite in direction to gravitational forces. Respirable particles reach this constant terminal or sedimentation velocity in less than 0.1 msec. Thus, particles are also removed as their terminal velocity causes them to strike the airway walls or alveolar surfaces.

3. Aerosol particles also undergo Brownian diffusion, a random motion caused by collisions of gas molecules with particles suspended in the air; this motion also causes the particles to cross streamlines and reach lung surfaces where they will deposit.

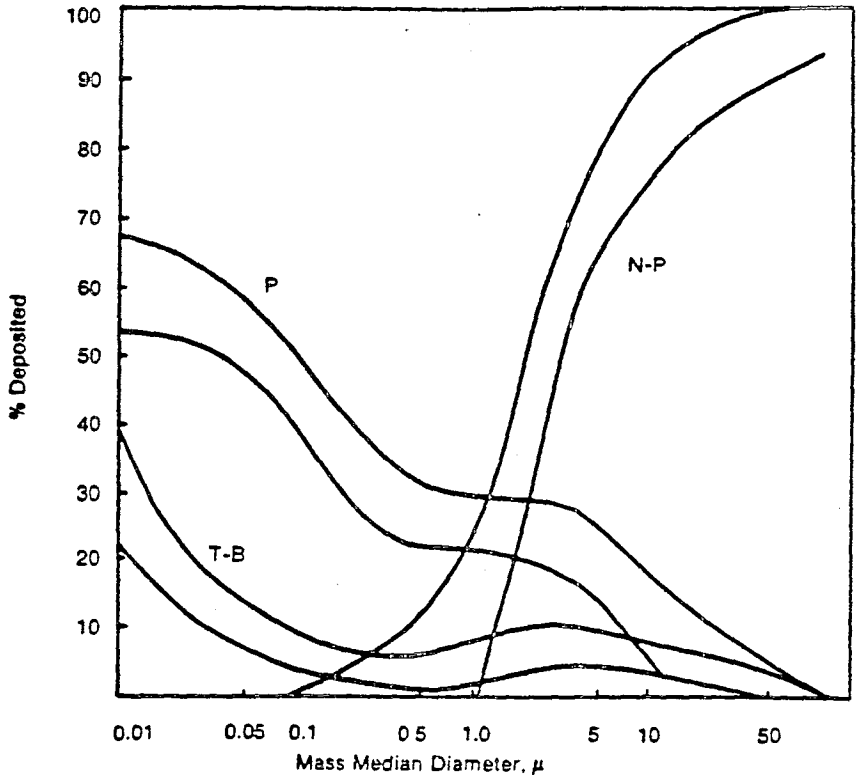
B. The effectiveness of these deposition mechanisms depends on: (1) the size distribution of aerodynamic diameters of the particles, (2) the pattern of breathing, and (3) the anatomy of the respiratory tract. These factors will determine not only the fraction of the inhaled particles that are deposited but also the site of deposition.

1. The effective aerodynamic diameters of particles determine the magnitude of forces acting on them. For example, while inertial and gravitational effects increase with increasing particle size, diffusion produces larger displacements as particle size decreases. Effective aerodynamic diameter is a function of particle size, shape, and density. In order to predict deposition patterns, it is essential to describe the distribution of aerodynamic diameters of particles in the aerosol. Two commonly-used parameters summarizing the size distribution are the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD).

2. Another factor modulating site and amount of deposition is breathing pattern. Minute volume defines the average flow velocity of the aerosol-containing air in the lung and the total number of particulates to which the lung will be exposed. Increasing the velocity of gas flow enhances deposition by inertial impaction. Respiratory frequency will affect the residence time of aerosols in the lungs and hence the probability of deposition by gravitational and diffusional forces. Changing lung volume will alter the dimensions of the airways and parenchyma.

3. The anatomy of the respiratory tract is important since it is necessary to know the diameters of the airways, the frequency and angles of branching, and the average distances to alveolar walls. For a given inspiratory or expiratory flow rate, airway anatomy determines local linear velocity of the air stream and the character of the flow. A significant change in the effective anatomy of the respiratory tract occurs when there is a switch between nose and mouth breathing. In addition to warming and humidifying the air, the nose prevents penetration of large particles and highly soluble gases to the remainder of the respiratory system. The narrow cross section of the airway here results in high linear velocities. The sharp bends in direction of airflow and the nasal hairs both promote impaction of aerosols. Particle deposition exhibits variability due to inter- and intra-species differences in lung morphometry; even within the same individual, the dimensions of the respiratory tract vary with changing lung volume, with aging, and with pathological processes.

C. The ICRP lung model (See reference 5) provides some predictions for the percentage deposition of particles for an adult human breathing a 1,450 ml tidal volume, 15 times a minute. Deposition in the nasopharynx ranges from 50.2% of the inspired particles with 2.0 μm MMAD to 95.6% of 20 μm particles. Deposition in the tracheobronchial compartment decreases from 3.6 to 1.0% as the MMAD increases from 2.0 μm to 20 μm and finally, deposition in the pulmonary compartment decreases from 21 to 2.6% as MMAD increases from 2.0 μm to 20.0 μm. The predictions of the ICRP lung model are summarized in the graph below:



–Aerosol deposition in respiratory tract. Tidal volume is 1,450 ml; frequency, 15 breaths per minute. Variability introduced by change of sigma, geometric standard deviation, from 1.2 to 4.5. Particle size equals diameter of mass median size. (Adapted from Task Group on Lung Dynamics')

III. Lung Clearance Mechanisms:

Clearance refers to the dynamic processes that physically expel particulates from the respiratory tract; it is the output of particulates previously deposited. Highly soluble particles dissolve rapidly and are absorbed into the blood from the respiratory tract. Their metabolism and excretion resemble that of an intravenously injected dose of the same material.

A. Ciliated Regions

1. Less soluble particles that are deposited on the mucus blanket covering pulmonary airways are moved toward the pharynx by the cilia. Also present in this moving carpet of mucus are cells and particles which have been transported from the non-ciliated alveoli to the ciliated airways. Similarly, particles deposited on the ciliated mucus membranes of the nose are propelled toward the pharynx. There, mucus, cells, and debris coming from the nasal cavities and the lungs meet, mix with salivary secretions, and enter the gastrointestinal tract after being swallowed. Since the particles are removed with half-times of minutes to hours, there is little time for solubilization of slowly dissolving materials. In contrast, particles deposited in the non-ciliated compartments have much longer residence times and hence, there, small differences in *in vivo* solubility can have great significance.

2. A number of factors can affect the speed of mucus flow. They may be divided into two categories: those affecting the cilia themselves and those affecting the properties of the mucus. The following aspects of ciliary action may be affected: the number of strokes per minute, the amplitude of each stroke, the time course and form of each stroke, the length of the cilia, the ratio of ciliated to non-ciliated areas, and the susceptibility of the cilia to intrinsic and extrinsic agents that modify their rate and quality of motion. The characteristics of the mucus may become critically important. The thickness of the mucus layer and its rheological properties may undergo wide variations. Typical mucus carpet flow rates in the major airways are 5-10 mm/min.

B. Non-Ciliated Regions

1. Particles deposited in the non-ciliated portion of the lungs are either moved toward the ciliated region, primarily within alveolar macrophages, or they enter the alveolar wall and accumulate in connective tissue, especially lymph nodes. Particles remaining on the surface are cleared with a biological half-time estimated to be twenty-four hours in humans, while particles that have penetrated into "fixed" tissues are cleared with half-times ranging from a few days to thousands of days. Therefore, the probability of particle penetration is critical in determining the clearance of particles from the non-ciliated regions of the lungs.

2. Particles removed by alveolar macrophages show a variety of patterns and half-lives which are dependent upon particle number, size, shape and surface reactivity. However, generally alveolar macrophages act to decrease the probability of particle penetration, thereby aiding clearance. These free cells, ultimately derived from the hematopoietic system, play the primary role in removal of dust particles and potentially pathogenic micro-organisms from the alveoli. Most free cells containing the deposited particles eventually reach the ciliated region of the lungs and are eliminated into the pharynx and swallowed.

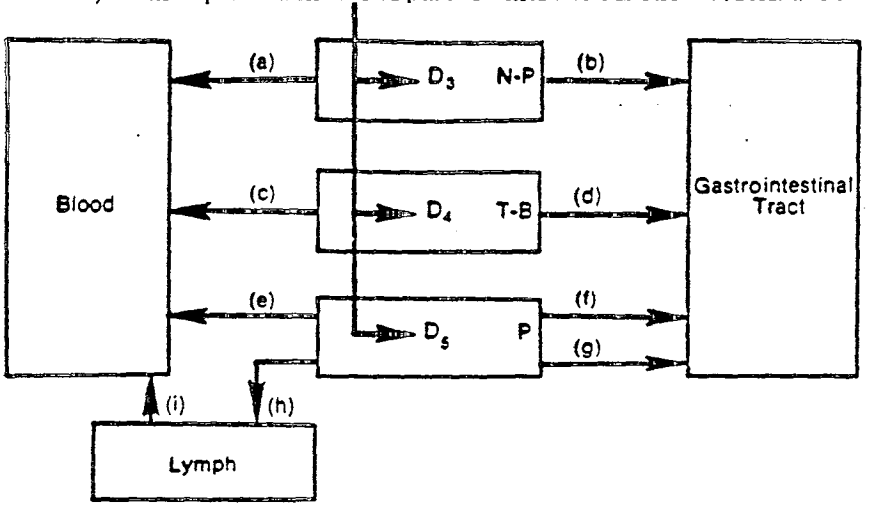
3. The digestive capacity of the pulmonary macrophage and its ample lysosomal endowment is reflected in its high content of hydrolytic enzymes. Although this clearly constitutes an important aspect of the lung's defensive posture, when kept in a chronically activated state, this

digestive capacity may serve to damage pulmonary tissues. Release of lysosomal enzymes, particularly proteases, from activated macrophages and polymorphonuclear leukocytes may be involved in the development of emphysema. Release may occur as a consequence of cell death, cell injury, or exocytosis. Other mediators released from these cells may also be involved in fibrogenesis. Since increased particle deposition acts to recruit additional macrophages and other cells, these untoward effects may be reinforced by increased dust deposition.

IV. Retention and particle excretion.

The actual amount of a substance in the respiratory tract at any time is called the retention. When the exposure is continuous, the equilibrium concentration (achieved when the clearance rate matches the deposition rate) is also the retention. Thus, the relative rate constants of deposition and clearance determine the equilibrium levels; it is the equilibrium level, or retention integrated over time, and the properties of the particle that are presumably related to the probability of a pathological response. The pathological consequences of dust retention may be a result of its allergic, irritant, carcinogenic, infective, or other properties. Continuing research focusing on the deposition and clearance of dusts and the significance of their retention is needed.

On the figure below, an example of a model of particle excretion is shown (Ref. # 5):



—Particle deposition sites and clearance processes based on ICRP lung model. Symbols are as follows: (a), uptake of material from N-P region directly into bloodstream; (b), clearance of all particulate matter from N-P region by ciliary-mucous transport; (c), absorption of material deposited on T-B surface into systemic circulation; (d), T-B clearance by ciliary-mucous action. Particles thus cleared go quantitatively to gastrointestinal tract; (e), direct absorption of material from pulmonary region into blood; (f) relatively rapid clearance of P region (in reality, coupled to ciliary-mucous transport system); (g), relatively slow clearance process, also coupled to N-P ciliary-mucous mechanism; (h), removal of matter into lymph system; and (i), secondary pathway in which particles cleared by pathway h are introduced into systemic blood. (Adapted from Task Group on Lung Dynamics[1])

Table 1.—Clearance Constants for Use With Lung Model*

Compartment	Pathway	Clearance Constants†		
		Class D	Class W	Class Y
N-P	(a)	4 min/0.50	4 min/0.10	4 min/0.01
	(b)	4 min/0.50	4 min/0.90	4 min/0.99
T-B	(c)	10 min/0.50	10 min/0.10	10 min/0.01
	(d)	10 min/0.50	10 min/0.90	10 min/0.99
P	(e)	30 min/0.80	90 days/0.15	360 days/0.05
	(f)	NA	24 hr/0.40	24 hr/0.40
	(g)	NA	90 days/0.40	360 days/0.40
	(h)	30 min/0.20	90 days/0.05	360 days/0.15
L	(i)	30 min/1.00	90 days/1.00	360 days/0.10

* Adapted from Task Group on Lung Dynamics.[1]

† First value is biological half-time; second, regional fraction. Lymphatic clearance for class Y compounds indicates that 10% regional fraction follows 360-day biological half-time. Remaining 90% is presumed to be permanently retained in nodes and subject only to radioactive decay.

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Table 1

ANATOMY OF EPITHELIAL BARRIERS

Interface with Environment	*Area (m^2)*	*Thickness from Environment-to-Blood (μm)*	*Organ Weight (kg)*
skin	**1.8**	**100-1000**	**12**
gastrointestinal	**200**	**8-12**	**7**
lungs	**140**	**0.2-0.4**	**0.8**

Table 2

FUNCTION OF EPITHELIAL BARRIERS

Interface with Environment	*Basal Blood Flow (liter/min)*	*Cell Turnover (days)*	*Basal Exposure Rate*
skin	**0.5**	**12**	**variable**
gastrointestinal	**1.4**	**3**	**2 kg/day**
lungs	**5.8**	**28**	**24 kg air/day**

Table 3

Browninan diffusion (root-mean-square) in 1 second compared with distance fallen in 1 second for unit density particles of different diameter *

	Particle Diameter (μm)	*Diffusion in 1 second (μm)*	*Distance Fallen in 1 second (μm)*
Settling greater in 1 s	**50**	**1.7**	**70,000**
	20	**2.7**	**11,500**
	10	**3.8**	**2,900**
	5	**5.5**	**740**
	2	**8.8**	**125**
	1	**13.0**	**33**
Diffusion greater in 1s	**0.5**	**20**	**9.5**
	0.2	**37**	**2.1**
	0.1	**64**	**0.81**
	0.05	**120**	**0.35**
	0.02	**290**	**0.013**
	0.01	**570**	**0.0063**

* *Temperature, 37°C; gas viscosity 1.9×10^{-5} Pa-s; appropriate correction factors applied for motion outside the range of validity of Stoke's Law.*